UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/035,420	10/25/2001	Sidney N. Wolfe	PP16022.004	2430

45853 7590 04/13/2006

CHIRON CORPORATION
INTELLECTUAL PROPERTY - R440
PO BOX 8097
EMERYVILLE, CA 94662-8097

EXAMINER	
SEHARASEYON, JEGATHEESAN	
ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 04/13/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/035,420	WOLFE ET AL.	
	Examiner	Art Unit	
	Jegatheesan Seharaseyon, Ph.D	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 February 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *5-9,13-17,19,20,26-43 and 45-49* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *5-9,13-17,19,20,26-43 and 45-49* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☒ Interview Summary (PTO-413) Paper No(s)/Mail Date. *included*.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 2/2/2006 has been entered. An action on the RCE follows.

2. Claims 20-30 are pending and under examination.

3. The text of those sections of Title 35, U. S. Code not included in this action can be found in a prior Office action.

4. Applicant's arguments filed 9/27/05 have been fully considered but are not persuasive.

Claim Rejections - 35 USC § 103, maintained

5. The rejection of claims 5-9, 13-17, 19, 20 and 26-49 under 35 USC § 103 as being obvious over Dorin et al. (U. S. Patent No. 5, 814, 485) in view of Hershenson et al. (U. S. Patent No. 5, 004, 605) and further in view of The Merck Index (1989) is maintained.

Applicants assert that they have discovered improved pharmaceutical formulations including monomeric interferon-β having a pH of about 3.0 to about 5.0 in an aspartic acid or sodium succinate buffer. However, Applicants have not provided any evidence to indicate that the formulations are improvements. Applicants are arguing an unexpected result without any evidence to support the assertion (MPEP § 716.02).

In response to applicant's argument that there is no suggestion/motivation to combine the references (see pages 8 and 9 of the response), the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, while it is true that Dorin et al. (U. S. Patent No. 5, 814, 485) disclose that the pH of the formulation is adjusted to between 6.0 and 7.5, there is no disclosure that would teach away from the present invention. Further Dorin et al. teach that the pH will be chosen not only to optimize the longevity of the IFN-β polypeptide but also to ease administration of the IFN-β polypeptide to humans (see column 13, lines 48-50), thus, providing the motivation to adjust the pH for optimal storage and/or administration. In addition, the teachings to adjust the pH to 3.0 to 5.0 is provided by Hershenson et al. (U. S. Patent No. 5, 004, 605), which states that stable pharmaceutical compositions suitable for parenteral administration to mammals is achieved keeping the β-interferon at a pH range of 2.0 to 4.0 in the substantial absence of detergents (see column 22, lines 14-24). Furthermore, MPEP § 2144.05 states that, in the case where the claimed ranges "overlap or lie inside ranges disclosed by the prior art" a prima facie case of obviousness exists. In re Wertheim, 541 F.2d 257, 191 USPQ 90 (CCPA 1976); In re Woodruff, 919 F.2d 1575, 16 USPQ2d 1934 (Fed.Cir. 1990) (The prior art taught carbon monoxide concentrations of "about 1-5%" while the claim was

limited to "more than 5%." The court held that "about 1-5%" allowed for concentrations slightly above 5% thus the ranges overlapped.). Furthermore MPEP § 21044.05 [R-3] states that "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." In re Aller, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955). Therefore, one of skilled in the art would be motivated to modify the pH range (3.0-5.0) to optimize the pharmaceutical compositions.

Applicants argues that "the combination of the teachings of '485 patent (pH range 6.5 to 7.5) with the '605 patent (teaching the use of glycine to formulate IFN- β) leads to an IFN- β formulation using glycine at a pH range of 6.0 to 7.5. Because the first pKa of glycine is 2.34 (see Merck Index), glycine is not a suitable buffer for formulations with a pH range of 6.0 to 7.5 (see page 10 of the response)". Thus, Applicants maintain that the '485 patent teaches away from such combination. This is not an accurate description of '485 patent because '485 patent does teach that amino acids (including glycine) may be added as a protectants (see column 13, lines 20-35). Furthermore as indicated previously Dorin et al ('485 patent) does teach that the pH will be chosen not only to optimize the longevity of the IFN-β polypeptide but also to ease administration of the IFN-β polypeptide to humans (see column 13, lines 48-50). This disclosure indicates that while the pH range of 6.0-7.5 is specifically stated, it also indicates other pHs are intended, namely those that provide for optimization of storage. Thus Dorin et al. provide clear motivation to modify the pH of the composition because long term storage is desirable.

With respect to Applicants arguments that there is no motivation to combine the teachings of '485 patent and '605 patent with that of The Merck Index teachings concerning the pKa of aspartic acid is not found to be persuasive. As indicated previously in the Office Action dated 11/8/04 (pg. 3), the Merck Index, p. 132, teaches that aspartic acid is a weak acid with a pKa useful in the pH range of Hershenson et al. Thus it would be obvious to one of ordinary skill in the art to substitute aspartic acid for the glycine Dorin et al., because the artisan of ordinary skill would recognize, based on the teachings of the Merck Index, that it would be equally effective for buffering at this pH. Thus, it is not an invitation to experiment as Applicant contends, because '485 and '605 patents clearly provide motivation to modify the composition. In addition, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). The Office agrees with Fiona et al (Exhibit A).

Finally, with respect to Applicants assertion that the instant method of formulating IFN-β yields compositions that are free of glycerol and polyethylene glycol polymers (see Applicants response filed 4/8/05, pg 9) is not found to be persuasive for reasons set forth in the Office Action dated 6/7/2005. While the '605 patent requires the use of a stabilizer, the instant claims do not exclude one for the reasons set forth above. In addition, MPEP §2111.03 states,

The transitional phrase "consisting essentially of" limits the scope of a claim to the specified materials or steps "and those that do not materially affect the basic and novel characteristic(s)" of the claimed invention. In re Herz, 537 F.2d 549, 551-52, 190 USPQ 461, 463 (CCPA 1976) (emphasis in original).For the purposes of searching for and

applying prior art under 35 U.S.C. 102 and 103, absent a clear indication in the specification or claimsof what the basic and novel characteristics actually are, "consisting essentially of" will be
construed as equivalent to "comprising." See, e.g., PPG, 156 F.3d at 1355, 48 USPQ2d at 1355 ("PPG could have defined the scope of the phrase consisting essentially of' for purposes of its patent by making clear in its specification what it regarded as constituting a material change in the basic and novel characteristics of the invention.").

Claim Rejections - 35 USC § 112 (new)

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6a. Claims 29, 34, 41 and 49 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. *This is a written description rejection.*

The specification discloses the IFN- β polypeptides of SEQ ID NO: 1 and SEQ ID NO: 2. This meets the written description and enablement provisions of 35 USC 112, first paragraph. However, the specification does not disclose all possible variants of IFN- β that has at least 80% amino acid identity to SEQ ID NO: 1. The claims as written, however, encompass IFN- β variant (805 identity to SEQ ID NO: 1) sequences including substitutions and deletions, which were not originally contemplated and fail to meet the written description provision of 35 USC 112, first paragraph because the written description is not commensurate in scope with the recitation of claims 29, 34, 41

and 49. The specification does not provide written description to support the genus encompassed by the instant claims.

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed" (*See Vas-Cath* at page 1116).

With the exception of IFN- β polypeptide described by SEQ ID NO: 1 and 2, the skilled artisan cannot envision all the detailed chemical structure of the claimed polypeptide sequences of the variants, regardless of the complexity or simplicity of the method of isolation.

Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. The polypeptide itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (CAFC 1993) and *Amgen Inc. V. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016. One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481, 1483. In *Fiddes v. Baird*, claims directed to mammalian FGF's were found unpatentable due to lack of written description for the broad class.

Therefore, only the IFN- β polypeptides described by SEQ ID NO: 1 and 2, but not the full breadth of the claims meets the written description provision of 35 USC 112, first paragraph. The species specifically disclosed are not representative of the genus because the genus is highly variant. As a result, it does not appear that the inventors were in possession of various polypeptides set forth in claims 29, 34, 41 and 49.

Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 USC 112 is severable from its enablement provision. (See page 1115.) Applicants are directed to the Revised Interim Guidelines for the Examination of Patent

Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 64, No. 244, pages 71427-71440, Tuesday December 21, 1999.

6b. Claims 29, 34, 41 and 49 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while enabling for IFN- β polypeptides of SEQ ID NO: 1 and 2, does not reasonably provide enablement for all variants IFN- β (80% identity to SEQ ID NO: 1) proteins including various substitution and deletions. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue. See *In re Wands,* 858 F.2d at 737, 8 USPQ2d at 1404. The factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue" include, but are not limited to: (1) the breadth of the claims; (2) the nature of the invention; (3) the state of the prior art; (4) the level of one of ordinary skill; (5) the level of predictability in the art; (6) the amount of direction provided by the inventor; (7) the existence of working examples; and (8) the quantity of experimentation needed to make or use the invention based on the content of the disclosure.

Despite knowledge in the art for producing variants of a given polypeptide with amino acid deletions, insertions or substitutions the specification fails to provide any

guidance regarding the changes/modifications contemplated and yet retain the function of the IFN- β claimed. There is no functional recitation. Furthermore, detailed information regarding the structural and functional requirements of the disclosed protein is lacking. Although it is accepted that the amino acid sequence of a polypeptide determines its structural and functional properties, predicting a protein's structure and function from mere sequence data remains an elusive task. The problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex. While it is known that many amino acid substitutions are generally possible in any given protein the positions within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of success are limited. Certain positions in the sequence are critical to the protein's structure/function relationship, e.g. such as various sites or regions directly involved in binding, activity and in providing the correct three-dimensional spatial orientation of binding and active sites. These or other regions may also be critical determinants of antigenicity. These regions can tolerate only relatively conservative substitutions or no substitutions (see Wells, 1990, Biochemistry 29:8509-8517; Ngo et al., 1994, The Protein Folding Problem and Tertiary Structure Prediction, pp. 492-495). However, Applicant has provided little or no guidance beyond the mere presentation of sequence data to enable one of ordinary skill in the art to determine, without undue experimentation, the positions in the protein which are tolerant to change (e.g. such as by amino acid substitutions or deletions), and the nature and extent of changes that can be made in these positions. Although the

specification outlines art-recognized procedures for producing and screening for active variants, this is not adequate guidance as to the nature of active derivatives that may be constructed, but is merely an invitation to the artisan to use the current invention as a starting point for further experimentation. Even if an active or binding site were identified in the specification, they may not be sufficient, as the ordinary artisan would immediately recognize that an active or binding site must assume the proper three-dimensional configuration to be active, which conformation is dependent upon surrounding residues; therefore substitution of non-essential residues can often destroy activity. Therefore, predicting which variants would retain the functions of the IFN- β protein is well outside the realm of routine experimentation. Thus, undue amount of experimentation would be required to generate changes/modifications of the polypeptide contemplated and yet retain the recited function of the IFN- β variant proteins claimed.

Applicants have not taught how one of skill in the art would use the full scope of polypeptides encompassed by the invention of claims 29, 34, 41 and 49. The specification as filed does not sufficiently teach one of skill in the art how to make and/or use the full scope of the claimed sequences. The amount of experimentation required to make and/or use the full scope of the claimed sequences would require trial and error experimentation to determine the functional sequences. Given the breadth of claims 29, 34, 41 and 49 in light of the unpredictability of the art as determined by the lack of working examples and shown by the prior at of record, the level of skill of the artisan, and the lack of guidance provided in the instant specification, it would require undue

experimentation for one of ordinary skill in the art to make and use the claimed invention.

7. No claims are allowable.

Contact Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jegatheesan Seharaseyon, Ph.D whose telephone number is 571-272-0892. The examiner can normally be reached on M-F: 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda Brumback can be reached on 571-272-0961. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

JS 04/06

CHRISTINE J. SAOUD
PRIMARY EXAMINER
Christine J. Saoud